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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/725,030	11/29/2000	Ashley Stuart Davis		8960

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EXAMINER	
LUKTON, DAVID	
ART UNIT	**PAPER NUMBER**
1654	

DATE MAILED: 10/31/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/725,030	DAVIS ET AL.	
	Examiner	Art Unit	
	David Lukton	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Pursuant to the response filed 8/18/05, no claim has been added, cancelled, or amended. Claims 26-29 remain pending.

Applicants' arguments filed 8/18/05 have been considered and found persuasive in part. The rejection of claims 26-29 as anticipated by Davis (*Neoplasia* 1(6) 498-507, 1999) is withdrawn.

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The response filed 5/6/05 contains the following statement:

> "As a preliminary matter, Applicants request that the previous request for priority to U.S. Serial No. 09/258,732 be withdrawn. Accordingly, the present application has no claim for priority."

Applicants are now required to provide a substitute oath/declaration (accompanied by the requisite fee) which makes no priority claim

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The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26-29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 26 recites that division of any and all cell types will be inhibited by IAABE. This would include fibroblasts, T-cells, red blood cells, lymphocytes, neuronal cells, epidermal cells, etc. It does not appear that descriptive support exists for inhibiting division of any and all cell types.

Claim 28 recites that IAABE can inhibit division of a helminth cell. However, there does not appear to be descriptive support for this. The following passage (page 2, last 5 lines) is noted:

> "In addition, the fact that so many other tubulin ligands have applications in anti-restenosis, anti-fungal, anti-helminths and anti-gout chemotherapies there is a strong likelihood that BAABE and IAABE will likewise have potential in these areas. In support of this hypothesis it was recently found that IAABE has anti-trypanosome activity (J. G. Bekesi, 1999), following this argument other diseases may be treatable with these compounds."

In response, applicants have argued the following:

> "the question of whether division or mitosis of any and all cell types within a helminth organism will be inhibited by IAABE is a question of enablement, not written description".

Applicants are incorrect about this. The fact is that the issue is <u>both</u> that of enablement and written description. This may or may not be true in the

general case, but it is true in the prosecution of application 09/725030.

Applicants have also argued because the specification (page 2) speculates that IAABE may have potential in the treatment of a helminth infection, it follows therefrom that the specification provides descriptive support for a method of inhibiting division of any and all cell types that occur within a helminth organism. Compounds which are effective against parasites, especially endoparasites, generally exert their effect on a specific biochemical process. Of course, if the endoparasite dies, then all cell division stops. But the point is that when an agent is effective at reducing the population of an endoparasite, it rarely (if ever) works by directly inhibiting division of all cell types within the organism. Thus, there is no implication in the specification that division of all cell types within a helminth will be inhibited.

Claim 28 recites that IAABE can inhibit division of a "cell involved in restenosis" and a "cell involved in gout". Certainly, there is no explicit recitation of the phrases at issue. But it also does not appear that the phrases are implied anywhere. Further, there is no explanation provided as to how or where one draws the line between a cell that is involved (in restenosis or gout) and a cell which is not. Similarly, there is no descriptive support for inhibiting division of a "cell involved in myelodisplasia syndrome" (claim 29).

In response to the foregoing, applicants have argued that descriptive support for

a "cell involved in restenosis" and a "cell involved in gout" can be found in original claim 7. However, applicants are not correct. First, this claim pertains to a compound which is not 3-IAABE. The arugment could stop there and be sufficient. But even if claim 7 had been drawn to a method of using 3-IAABE, claim 7 would still not provide descriptive support for a "cell involved in restenosis" or a "cell involved in gout". Claim 7 recites only "therapeutic potential" in the treatment of restenosis or gout, not a method of inhibiting division of a "cell involved in restenosis" or a "cell involved in gout". Which cells are involved? What are the criteria for determining involvement? None of this is made clear by the specification. Applicants have argued that if a cell is producing too much uric acid it would qualify as a "cell involved in gout". Which cells would that be, and how much is too much? Suppose that a given person is showing no symptoms of gout, and is healthy by any physical test. But suppose also that one type of cell was producing "too much" uric acid, while other cell types were producing "too little". Is it applicants contention that the 3-IAABE would "know" that it's supposed to inhibit division of those cells that were producing "to much" uric acid, while leaving the other cells (which are producing were producing "too little") unaffected? With regard to restenosis, applicants have stated simply that if a cell is involved in arterial re-narrowing, then that cell qualifies as a "cell involved in restenosis". Applicants have declined to speculate, however, as to which cell types this might

be. Applicants have even declined to speculate as to the causes of the re-narrowing. And even if applicants were willing to offer such speculation, the specification would still be as it was when filed, without the benefit of applicants' new insights.

As for inhibiting a "cell involved in myelodisplasia syndrome", applicants have argued that descriptive support can be found on page 12 of the specification. However, the term at issue does not appear on page 12. It is noted that on this page it is asserted that IAABE inhibited growth of CEM leukemic cells, but this is far different from inhibiting a "cell involved in myelodisplasia syndrome".

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Claims 26-29 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 26-28 recite that the division of any cell type can be inhibited. This would include any and all cells, healthy or not. Applicants have demonstrated inhibition of mitosis of a few cell types including CEM cells, EL4 lymphoma cells, and prostate carcinoma cells. However, it does not follow therefrom that mitosis of any and all cell types will be inhibited.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988) the factors to consider in evaluating the need (or

absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims.

It is the examiner's assertion that merely because one can demonstrate inhibition of mitosis of 2 or 3 tumor cell types, it does not follow therefrom that mitosis of any and all cell types will be inhibited. One can look to literature on apoptosis inhibition for indications of such unpredictability. For example, Fang X. (*Biochemical Journal* **352 Pt 1** 135-43, 2000) discloses that lysophosphatidic acid inhibits apoptosis in fibroblasts; at the same time, Steiner M. R. (*Annals of the New York Academy of Sciences* **905** 132-41, 2000) discloses that lysophosphatidic acid induces apoptosis in neuronal cells. Thus, if a determination is made that a given compound will inhibit apoptosis of a given cell type, the skilled artisan cannot predict the cell types in which apoptosis will be inhibited, and the cell types in which apoptosis will be induced. This conclusion is reinforced by the findings of Tsuchiyama Y (*Kidney International* **58** (5) 1941-52, 2000) who discloses that while dexamethasone induces apoptosis in both CD8+ cells and CD4+ cells, Galectin-9 induces apoptosis in CD8+ cells, but fails to induce apoptosis in CD4+ cells. The mechanism of action of the compounds disclosed in the foregoing references may not be identical to that of

IAABE, but the point is that if one can demonstrate inhibition of cell division in one cell type, one cannot "predict", on that basis, that inhibition of mitosis of all cell types will occur.

Further, there is no guidance as to which cell types will be affected by the IAABE. In fact, the implication of the specification is that only certain types of cancer cells and cells of parasitic organisms will be affected. This conclusion is reached because the specification conveys that mammals afflicted with certain types of cancer can be successfully treated by the disclosed compounds. If the IAABE were effective to inhibit mitosis of all cell types, (e.g., fibroblasts, T-cells, red blood cells, dermal cells), the ensuing illness induced thereby would be more severe that the disease prior to treatment. Thus, the implication of the specification is that only certain cell types are affected by the IAABE, and not others, but the specification does not explain which cell types will be affected and which will not. Accordingly, guidance for the claimed invention is lacking. [Claim 29 is rejected because of the phrase "cell involved in myelodisplasia syndrome"].

In view of the absence of guidance, insufficiency of working examples, nature of the invention, state of the prior art, or unpredictability of the art, and breadth of the claims, "undue experimentation" would be required to inhibit mitosis in any and all cell types.

In response to the foregoing, applicants have begun by arguing that the outcome of chemical reactions is not necessarily unpredictable. The validity of this particular assertion is left unchallenged by the examiner. However, what may be true about chemical reactions does not necessarily apply in biochemistry or pharmacology. Next, applicants have argued that they should not have to provide test data for every species covered by the claims. In response, the examiner is not requiring such. At the same time, however, a demonstration that applicants can inhibit division of a small fraction of 1% of all known cell types hardly qualifies as an enabling disclosure.

Next, applicants have argued that the examiner has not provided a reasonable explanation as to why a claim drawn to a method of inhibiting division of "a cell" might not be enabled. The examiner's first point, while critical, is semantic, and quite simple. And that point is that the indefinite article ("a") within the phrase "division of a cell" encompasses any cell and all cells. Throughout the discussion, applicants have attempted to blur the line between this broad meaning of "a cell", and the much narrower meaning which is also encompassed (i.e., one cell type). But the fact remains that the phrase "a cell", when used in claim 26 (for example) refers to all cells, and any cells. As simple as this point is, it is an important one for the discussion going forward.

Applicants have continued by arguing that the examiner has made reference to failures of compounds that are "completely unrelated" to IAABE, and that because

of this, the examiner has failed to meet his burden of providing a "reasonable explanation" as to why a claim drawn to a method of inhibiting division of any and all cells is not enabled. Applicants are quite correct that the examiner has not provided a reference which shows that IAABE itself will fail to inhibit division of a given cell type. But this is not a requirement in order to sustain an enablement rejection. The key issue here is "unpredictability". Applicants are attempting to extrapolate from a showing that mitosis of CEM cells, EL4 lymphoma cells, and prostate carcinoma cells can be inhibited, to an assertion that mitosis of any and all cell types can be inhibited. The question is whether such an attempted extrapolation is predictable or not. The question is not whether the examiner can provide definitive proof of failure. If applicants genuinely believe that there exists a court opinion or statute which holds that an examiner must provide definitive proof of failure in order to sustain an enablement rejection, applicants should cite the same. Otherwise, the assertion, or implication, that such a court opinion or statute exists is meaningless. The references cited by the examiner demonstrate that there exist compounds, patentably distinct from that cited in the instant claims, which exhibit opposite effects on apoptosis in different cell types. Does this prove beyond all doubt that applicants invention will fail? Of course not. But that is not the legal standard which must be met. The examiner has indeed made out a *prima facie* case for "unpredictability". It is known in the art that other compounds will

exhibit different effects on mitosis, depending on the cell type. In some cell types mitosis will be increased, in other cell types mitosis will be decreased, and other cell types will be largely unaffected. The burden now shifts to applicant to explain why it is that the conclusion of unpredictability might not be correct. One place to start might be to provide examples of compounds which are indeed effective to inhibit mitosis of any and all cell types. This would correspond to another of the "Forman factors" (i.e., state of the prior art). If it were well known at the time of the invention (and it was certainly not known at all) that if a compound were effective to inhibit mitosis of 2 or 3 cell types, then that compound will be effective to inhibit mitosis of all cell types, it would behoove applicants to bring such to the fore. If applicants can provide such a reference, it will not be definitive, but at least applicants would be in a position to make an opposing argument. At present, there is no evidence or indication that any such compounds are known.

Applicants have also responded to the examiner's assertion (essentially) that the "cure will be worse than the disease", i.e., that if it is true that mitosis of all cell types will be inhibited, the IAABE will induce an illness that was worse than what was present prior to administration. In response, applicants have made two arguments: (a) it is not the examiner's role to evaluate the efficacy of a given compound to which claims are drawn, and (b) it is not the examiner's role to evaluate the safety of a given compound to which claims are drawn. As it

happens, applicants second point is true in nearly all cases. There is one principal exception, and that is if the examiner can provide evidence of significant harm or toxicity. That evidence actually comes from applicants themselves. Applicants have argued that their compound will attack all cell types, and will spare no cell type the ravages of the compound. Of course, death of the patient is far from inevitable. If the dosage is sufficiently low, then the patient will not become more ill than he was before the treatment. But then, the compound will be ineffective. Thus, given applicants assertion that the compound is indiscriminant, one of the following must be true: (a) the compound will not be effective to inhibit division of all cell types, or (b) the compound will be lethal, or at the very least, cause an illness which is much more severe that was the case previously. As for applicants assertion that it is not the examiner's role to evaluate the efficacy of a given compound to which claims are drawn, applicants are simply incorrect. The §112, first paragraph statute empowers examiners to make just that determination.

The rejection is maintained.

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Claims 26-29 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- The claims assert that inhibition of cell division can be achieved by contacting a cell with IAABE. The claims, however, are indefinite as to whether an effective amount is used, or whether an amount which is less than effective is used. Is it the case that the claims encompass the use of ineffective amounts of the IAABE...?

  Applicants have argued that it would be illogical to assume that the claims encompass amounts of the IAABE which are less than effective. However, it is quite often the case that an applicant will seek the broadest scope possible in their claims. In pursuit of this goal they will frequently make assertions about what limitations are implicit. As it happens, not all of their assertions are logical. In the instant case, it may be that applicants do not want to relinquish those embodiments in which the amount of compound used is insufficient to inhibit cell division. If that is the case, it would be understandable for applicants to argue that such embodiments do not exist. Yet they do exist, and the rejection is maintained.

- Claim 28 recites the phrase "cell involved in restenosis" and "cell involved in gout". Claim 29 recites the phrase "cell involved in myelodisplasia syndrome". What are the criteria for deciding whether a cell is at least tangentially involved in one of the recited disorders or not? In considering the various biochemical processes involved, how far "upstream" or "downstream" can one go in determining "involvement"...? Applicants have declined to address the key issue here, which is that of how far "upstream" or "downstream" can one go in determining "involvement"...? Instead, applicants have merely cited a tautology, which is that if a cell is involved, then it is involved. As applicants appear not to appreciate, the physiology and biochemistry of disease is highly complex. It is rarely the case that when one cell type goes awry, other cell types are not effected. Diseases involve one or more aspects of the immune system, the endocrine system, the circulatory system, the nervous system and the digestive system, to name a few. For example, if the level of interleukin 4 is altered in a given disease state, would applicants argue that the cell types which produce this IL-4 are "involved" in the disease? If a person is stricken with cancer, would applicants argue that T cells and B cells are involved, or not involved? Would applicants want to induce immunosuppression in a cancer patient?

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THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). The practice of automatically extending the shortened statutory period an additional month upon filing of a timely first response to a final rejection has been discontinued by the Office. See 1021 TMOG 35.

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED AND ANY EXTENSION FEE PURSUANT TO 37 CFR 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, can be reached at (571)272-0974. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

D. Lukton

DAVID LUKTON
PATENT EXAMINER
GROUP 1800